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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,971	09/24/2003	Dan-Ning Hu	A35422 073513.0102	7023

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,971	HU ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 19 is objected to because of the term "comprisingcomprising". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 8, it is unclear what is encompassed by the phrase "cAMP-elevating agent is selected from the group consisting of α-melanocyte stimulating factor, adrenaline, and L-epinephrine". This is because it is known in the prior art that terms "adrenaline" and "epinephrine" refers to the same molecule as evidenced by the teachings of Gruber et al. (US 5,925,682, see col. 2, lines 22-23), particularly as claimed the cAMP-elevating agent is a natural and physiological agent. Therefore, as written claim 8 recites an improper Markush group. Clarification is requested because the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 8-9, 11-12, 16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Swope et al. (Experimental Cell Research 217:453-459, 1995).

Swope et al. teach a method for the preparation of normal human melanocytes obtained from either neonatal foreskins or adult breast skin, comprising the step of separating the epidermis from the underlying dermis and resulting cell suspensions from both tissues were plated in culture flasks for studying (page 454, col. 2, first paragraph). Swope et al. further teach the use of a modified growth culture medium comprising MCDB153, 5% heat-inactivated fetal bovine serum, 5 ug/ml insulin, 1 ug/ml transferrin, 1ug/ml alpha-tocopherol, 0.6 ng/ml human recombinant basic fibroblast growth factor, 1% penicillin-streptomycin, α-melanocyte stimulating hormone, and endothelin-1, with the last two components substitute for bovine pituitary extract and TPA, respectively (page 454, col. 2, first four paragraphs and Fig. 1). Swope et al. specifically teach that the growth rates of melanocytes maintained in the presence of α-melanocyte stimulating hormone, and endothelin-1 were comparable to those of melanocytes from the same strain maintained in the presence of TPA and BPE (Fig. 2), but their modified growth medium is advantageous in that it lacks nonphysiologic and potentially hazardous

mitogens such as TPA and cholera toxin, and that it diminishes the dependency on variable, undefined constitutents such as BPE, and allows for rapid and long-term proliferation of melanocytes for extensive experimental or clinical uses including for the transplantation into the skin of patients with vitiligo (page 454, col. 1, bottom of first full paragraph; page 457, col. 2, top paragraph of the Discussion section).

The teachings of Swope et al. meet all the limitation of the instant claims. Accordingly, the reference anticipates the instant claims.

Claims 1-6, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Yanase et al. (U.S. 5,916,809) as evidenced by Swope et al. (Experimental Cell Research 217:453-459, 1995).

Yanase et al. disclose a medium for culturing normal human epidermal melanocytes *in vitro*. The medium comprises a basal medium for culturing animal cells (e.g, HAM F12, RPMI1640, Dulbecco's modified of Eagle's MEM, col. 2, lines 53-58), one or more growth factors useful for growth of human melanocyte (e.g, EGF, bFGF, IL-1, TGF-alpha, col. 5, lines 1-5), serum (e.g, fetal bovine serum, col. 5, lines 6-14), biological materials such as bovine pituitary extract, bovine hypothalamus extract, bovine cerebrum extract and albumin, insulin, PMA, heparin, cholera toxin, hydrocortisone (col. 5, lines 16-20), and antibiotics such as gentamicin sulfate, amphotericin B, penicillin, mitomycin and others (col. 5, lines 20-23). The bovine pituitary extract used in the cultured medium of Yanase et al. contains α-melanocyte stimulating hormone (a natural, physiological cAMP-elevating agent) which stimulates

adenylate cyclase as evidenced by the teachings of Swope et al. (page 454, col. 2, second paragraph).

Accordingly, the teachings of Yanase et al. meet the limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu et al. (Exp. Eye Res. 71:217-224, 2000).

Hu et al. teach the preparation of a melanocyte culture medium comprising the addition of cAMP-elevating isoproterenol into a complete FIC medium containing F12 basal medium supplemented with 10% FBS, glutamine, bFGF, IBMX, cholera toxin and gentamicin (page 218, col. 1, second paragraph; col. 2, third paragraph; and page 219, col. 2, bottom of first paragraph).

Please note the intended use for the composition is not given any patentable weight in light of the prior art. Accordingly, the culture medium taught by Hu et al. meets all the limitation of the composition claimed by the instant claims.

Accordingly, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-9 and 11-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (J. Dermatology 27:434-439, 2000) in view of Swope et al. (Experimental Cell Research 217:453-459, 1995).

Chen et al. teach a method for transplanting cultured autologous melanocytes onto laser-abrased vitiliginous areas of human patients in need thereof (see abstract). The method comprises the steps: (a) isolation of melanocytes from a small specimen of normally pigmented skin obtained via a suction blister, and a suspension of epidermal cells was obtained after excised roofs of blisters were enzymatically and mechanically treated (page 435, col. 1, second paragraph); (b) culturing epidermal cells in a modified melanocyte medium consisted of Ham's F12 nutrient mixture supplemented with gentamicin, recombinant human bFGF, fetal calf serum, isobutylmethylxanthine (IBMX) and cholera toxin (page 435, col. 1, bottom of second paragraph); (c) cultured melanocytes were treated on the third day of culture with geneticin for three consecutive days to inhibit the growth of keratinocytes and fibroblasts (page 435, col. 2, top of first

paragraph); and (d) confluent melanocytes were harvested and applied to laser denuded area of treated patients (page 435, col. 2, last two paragraphs). Chen et al. also teach that most patients experienced complete re-pigmentation after about one month, and that the presence of cAMP-elevating agents IBMX and cholera toxin is essential for the growth of epidermal melanocytes in the absence of TPA (page 438, col. 1, bottom of first paragraph).

Chen et al. does not teach specifically the use of a melanocyte culture medium containing a physiological cAMP elevating agent in the form of α-melanocyte stimulating hormone to expand cultured autologous melanocytes in their method.

However, at the filing date of the present application (9/24/03) Swope already teach a modified melanocyte culture medium comprising MCDB153, 5% heat-inactivated fetal bovine serum, 5 ug/ml insulin, 1 ug/ml transferrin, 1ug/ml alpha-tocopherol, 0.6 ng/ml human recombinant basic fibroblast growth factor, 1% penicillin-streptomycin, α-melanocyte stimulating hormone, and endothelin-1, with the last two components substitute for bovine pituitary extract and TPA, respectively (page 454, col. 2, first four paragraphs and Fig. 1). The effects of α-MSH are known to be mediated by stimulation of adenylate cyclase activity, increased cAMP synthesis, and activation of protein kinase A (page 454, col. 1, middle of first full paragraph). Swope et al. also teach that the growth rates of melanocytes maintained in the presence of α-melanocyte stimulating hormone, and endothelin-1 were comparable to those of melanocytes from the same strain maintained in the presence of TPA and BPE (Fig. 2), but their modified growth medium is advantageous in that it lacks nonphysiologic and potentially

hazardous mitogens such as TPA and cholera toxin, and that it diminishes the dependency on variable, undefined constitutents such as BPE, and allows for rapid and long-term proliferation of melanocytes for extensive experimental or clinical uses including for the transplantation into the skin of patients with vitiligo (page 454, col. 1, bottom of first full paragraph; page 457, col. 2, top paragraph of the Discussion section).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Chen et al. by utilizing a modified melanocyte culture medium disclosed by Swope et al. to expand autologous melanocytes prior to transplanting them into patients with segmental vitiligo due to the advantages offered by the modified melanocyte culture medium of Swope of et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the modified melanocyte culture medium taught by Swope et al. is not only comparable to a melanocyte medium containing TPA and BPE for maintaining the growth rate of melanocytes *in vitro,* but it lacks nonphysiologic and potentially hazardous mitogens such as TPA and cholera toxin, one of which (cholera toxin) is present in the culture medium utilized by Chen et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Chen et al., Swope et al., and a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claims 1, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (J. Dermatology 27:434-439, 2000) in view of Swope et al. (Experimental Cell Research 217:453-459, 1995) as applied to claims 1-6, 8-9 and 11-19 above, and further in view of Hu et al. (Exp. Cell Res. 217:453-459, 1995).

The teachings of Chen et al. and Swope et al. have been discussed above. However, none of the references teach the use of L-epinephrine as a natural, physiological cAMP-elevating agent.

However, at the filing date of the present application Hu et al. already teach that c-AMP elevating agents: epinephrine, isoproterenol, salbutamol and metaproterenol (adrenergic agonists that can activate β2-adrenoceptors) substantially stimulated growth and melanogenesis of cultured human uveal melanocytes in cAMP-deleted medium, a medium without IBMX and cholera toxin (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to include c-AMP elevating agents such as epinephrine, isoproterenol, salbutamol and metaproterenol taught by Hu et al. in the melanocyte culture medium of the combined teachings of Chen et al. and Swope et al. because they are already demonstrated to be useful for melanocyte growth and melanogenesis.

An ordinary skilled artisan would have been motivated to carry out the above modification because the aforementioned c-AMP elevating agents, including epinephrine, are found to stimulate growth and melanogenesis of human melanocytes in a culture medium absent of IBMX and cholera toxin, both of which are nonphysiologic with the later is a potentially hazardous mitogen as already noted by Swope et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of teachings of Chen et al., Swope et al., and Hu et al., coupled with a high level of skill of an ordinary skilled artisan.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Claims 1, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanase et al. (U.S. 5,916,809) as evidenced by Swope et al. (Experimental Cell Research 217:453-459, 1995) in view of Hu (Pigment Cell Res. 13 Suppl 8:81-86, 2000).

Yanase et al. disclose a medium for culturing normal human epidermal melanocytes *in vitro*. The medium comprises a basal medium for culturing animal cells (e.g, HAM F12, RPMI1640, Dulbecco's modified of Eagle's MEM, col. 2, lines 53-58), one or more growth factor useful for growth of human melanocyte (e.g, EGF, bFGF, IL-1, TGF-alpha, col. 5, lines 1-5), serum (e.g, fetal bovine serum, col. 5, lines 6-14), biological materials such as bovine pituitary extract, bovine hypothalamus extract, bovine cerebrum extract and albumin, insulin, PMA, heparin, cholera toxin, hydrocortisone (col. 5, lines 16-20), and antibiotics such as gentamicin sulfate, amphotericin B, penicillin, mitomycin and others (col. 5, lines 20-23). The bovine pituitary extract used in the cultured medium of Yanase et al. contains α-melanocyte stimulating hormone (a natural, physiological cAMP-elevating agent) which stimulates

adenylate cyclase as evidenced by the teachings of Swope et al. (page 454, col. 2, second paragraph).

However, Yanase et al. do not teach specifically that hepatocyte growth factor and basic fibroblast growth factor to be present in the culture medium.

At the filing date of the present application, Hu already teaches that hepatocyte growth factor stimulates melanogenesis and/or growth of human melanocytes in cultures (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to include hepatocyte growth factor in the culture medium taught by Yanase et al. because HGF has been shown to stimulate melanogenesis and/or growth of human melanocytes *in vitro* by Hu, and Yanase et al. specifically teach that one or more growth factor useful for growth of human melanocyte can be added in their culture medium (col. 1, lines 64-65).

An ordinary skilled artisan would have been motivated to include HGF in the culture medium of Yanase et al. because HGF stimulates melanogenesis and/or growth of human melanocytes and since Yanase et al. specifically teach that one or more growth factor useful for growth of human melanocyte can be added in their culture medium (col. 1, lines 64-65).

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER